Public Health Goal for Bentazon In Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without

regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR BENTAZON IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 200 ppb (parts per billion) is developed for bentazon 3-isopropyl-1H-2, 1,3-benzothiadiazin-4 (3H)-one 2,2-dioxide in drinking water. The PHG is based on non-carcinogenic effects such as clinical signs of toxicity, hematological changes, depressed body weight and intestinal disturbances identified in a chronic dog study (Allen et al., 1989). The no-observed-adverse-effect-level (NOAEL) identified in this study was 3.2 mg/kg-day and the lowest-observed-adverse-effect-level (LOAEL) 13.1 mg/kg-day. The PHG was calculated assuming an adult body weight of 70 kg, a water consumption rate of 2 L/day and 20% exposure to bentazon from drinking water, and using an uncertainty factor of 100 to account for inter- and intra-species extrapolation from a chronic animal study to humans.

INTRODUCTION

The purpose of this document is to support the development of a PHG for bentazon. Bentazon is not currently regulated under the Safe Drinking Water Act (SDWA). Therefore, no federal Maximum Contaminant Level (MCL) has been established by the U.S. Environmental Protection Agency (U.S. EPA). The California MCL for bentazon is 18 ppb following the earlier recommendations of this office (OEHHA) for the Proposed Maximum Contaminant Level (PMCL) (DHS, 1988). However, the availability of a more complete toxicological database for this chemical leads us to recommend a change in the level.

Bentazon was classified as a "Group E" carcinogen, which denotes evidence of non-carcinogenicity for humans, by U.S. EPA's Health Effects Division Carcinogenicity Peer Review Committee (6/26/91) (U.S. EPA RED, 1994).

In this document, we evaluate data on the toxicity of bentazon, primarily by the oral route, and include information available since the previous assessment (DHS, 1988). With the exception of a chronic toxicity study in dogs (Allen et al., 1989) new data on bentazon useful for risk assessment are very limited. Our review of the data on bentazon includes current online information available in RTECS, IRIS and HSDB (1998). To determine a public health-protective level of bentazon in drinking water, relevant studies were identified, reviewed and evaluated.

CHEMICAL PROFILE

Chemical Identity

Bentazon is a member of the thiadiazine group. It consists of a double ring structure, with an aromatic and a heterocyclic ring containing nitrogen and sulfur atoms. The chemical formula, structure, synonyms and identification numbers are listed in Table 1.

Physical and Chemical Properties

Important physical and chemical properties of bentazon are given in Table 2. Bentazon (technical) is only slightly soluble in water and is poorly volatile. Solubility will differ with the type of bentazon. Sodium bentazon, the form that is commercially available, is much more soluble. When heated to decomposition bentazon (technical) emits very toxic fumes of sulfur oxides and nitrogen oxides (SO_X and NO_X) (Sax, 1984).

Uses

Bentazon is also known by the trade name Basagran. It is a selective post-emergence herbicide used to control many broadleaf weeds and sedges primarily by contact action in most graminous and many large seeded leguminous crops such as food and feed crops including alfalfa, beans, corn, peanuts, peas, asparagus, cereals, peppers, peppermint, rice and sorghum. It is also used on two terrestrial nonfood crops: ornamental lawns and turf. It has little effect on germinating seeds, and is not used pre-emergence (Worthing and Walker, 1987).

Mode of Action

Bentazon is a benzothiadiazinone contact herbicide acting as a photosynthetic electron transfer inhibitor. Its selectivity is based on the ability of the crop plants to quickly metabolize bentazon to 6-OH- and 8-OH-bentazon and conjugate it with sugar. Since most weeds do not possess this metabolic ability, their photosynthesis is disrupted and the weeds die.

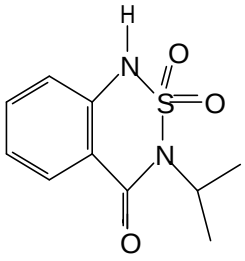
Table 1. Chemical Identity of Bentazon

Chemical name	3-isopropyl-1H-2 1,3-benzothiadiazin-(3H)-one 2,2-dioxide
Synonyms	1H-2, 1,3-benzothiadiazin-4 (3H)-one, 2,2 dioxide, 3-isopropyl; 1H-2, 1,3-benzothiadiazin-4 (3H)-one, 3-isopropyl 2,2-dioxide; 1H-2, 1,3-benzothiadiazin-4 (3H)-one, 3-(1-methylethyl), 2,2-dioxide and 3-(1-methylethyl)-(1H)-2,1,3-benzothiadiazin-4 (3H)-one 2, 2-dioxide)
Common names	Bentazon (ANSI, CSA, WSSA); Bentazone (ISO, BSI, JMAF); Bendioxide (So. Africa)
Other names	Basagran, Pentazone, Pledge.
Registered trade name	Manufacturing-use product: “Bentazon Manufacturer’s Concentrate” (46% sodium bentazon, liquid). EPA Reg. No. 7969-42. End-use product: “Basagran Postemergence Herbicide” (liquid concentrate containing 42% sodium bentazon). EPA Reg. No. 7969-45. End-use product: “Laddock Postemergence Herbicide” (flowable liquid concentrate” containing 18.52% sodium bentazon). EPA Reg. No. 7969-54.

Table 1. Chemical Identity of Bentazon (Continued)

Chemical formula	$C_{10}H_{12}N_2O_3S$
Wiswesser line notation	T66 BMSWNVJ DY1 (HSDB, 1998)

Chemical structure



Bentazon

Identification numbers

Chemical Abstracts Service (CAS) Registry numbers	25057-89-0 bentazon 50723-80-3 sodium bentazon
NIOSH Registry of Toxic Effects of Chemical Substances (RTECS)® number:	NIOSH/DK9900000
U.S. EPA Office of Pesticide Programs Chemical Code:	103901, sodium bentazon 275200, bentazon technical
Hazardous Substances Data Bank (HSDB) number:	3430
Registry of Toxic Effects of Chemical Substances (HCDB) Number:	DK9900000

Table 2. Physical and Chemical Properties of Bentazon

Property	Value	References
Molecular weight	240.30 g/mol	RTECS
Color	Colorless	Meister, 1998
Physical state	crystals	Tomlin, 1994
Odor	Odorless	Spencer, 1982
Melting point	approx. 138^{o}C	Meister, 1998
Flash point	greater than 100^{o}C	Weed Sci. Soc. Am., 1983
Vapor pressure	1.7 x 10^{-6} mm Hg (20^{o}C)	Worthing et al., 1987
Corrosivity	Not corrosive	Humburg, 1989
Density/Specific Gravity	1.47	Budavari, 1989
Dissociation Constants:	pKa = 3.3 at 24^{o} C	Tomlin, 1994
Solubility (technical bentazon) (w/w) at 20^{o}C		
water	570 mg/L	Huber and Otto, 1994
Mean K_D value:	0.6 cm^3/g (0.18 to 3.06)	ibid.
Mean K_{OC} value:	42 cm^3/g (13.3 to 175.6)	ibid.
Acetone	150.7%	DHS, 1988
Benzene	3.3%	ibid.
Chloroform	18%	ibid.
Ethanol	86.1%	ibid.
Log K_{OW} value:	-0.456 at pH 7.22^{o} C	Huber and Otto, 1994

Manufacturing information

Bentazon is manufactured by the reaction of anthranilic acid with isopropyl sulfamoyl chloride to produce N(isopropylsulfamoyl) anthranilic acid which is then cyclisized with phosgene to give bentazon (Sittig, 1980).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Soil

Bentazon degradation in soil is mainly controlled by oxidative mineralization to CO_2 mediated by microbial processes with subsequent residue incorporation into soil organic matter such as humins, humic acid, and fulvic acids (Huber and Otto, 1994). Bentazon has a low binding affinity to soil (K_d 0.176 to 3.056) and therefore is expected to leach into the ground and undergo runoff to surface waters. Leaching of bentazon through the soil appears to be a major route of dissipation in the environment. Phenyl-ring labeled bentazon applied at a rate of 20 lb/A (pounds/acre) degraded in mineral soils with a half-life of 24 days in clay loam soil, 31 days in loamy sand soil, and 65 days in sandy loam soil. In flooded sandy loam soil and rice clay soil phenyl-labeled bentazon did not degrade under anaerobic or aerobic conditions (U.S. EPA RED, 1994).

The first step in the aerobic, microbially induced degradation of bentazon in soil is a hydroxylation of the active ingredient molecule on the phenyl ring in the 6- or 8-position. This hydroxylation is carried out by several fungal species. The direct detection of 6-OH and 8-OH-bentazon in the soil is difficult because both of these intermediates are further metabolized microbially, more quickly than they can be produced as a result of the hydroxylation of bentazon. The more stable degradates of bentazon in soil are 2-amino-N-isopropyl benzamide (AIBA) and N-methylbentazon. AIBA is considered very mobile but not persistent. In soil it is very prone to microbial mediated degradation. N-methylbentazon is not mobile (Huber and Otto, 1994)

All intermediate products in the bentazon degradation process give rise to free radicals that readily bind or polymerize onto reactive groups of humins and become part of the humus structure. A major part of the ^{14}C activity originally incorporated in the aromatic ring of bentazon is quickly recovered as mineralized $^{14}CO_2$. Consequently, neither of the bentazon degradates pose a threat to the environment, including ground water. At a practical level only bentazon itself can be considered for environmental analysis since intermediate stages in its degradation process are difficult to measure analytically because of their rapid conversion rate (Huber and Otto, 1994; U.S. EPA RED, 1994).

Water

Bentazon degradation in an aquatic environment seems to be dependent on photolysis (U.S. EPA RED, 1994). This thesis is supported by studies on the photodegradation of bentazon in aqueous solutions with light resembling sunlight and in the presence of catalytic quantities of titanium dioxide (Pelizzetti et al., 1989). Within minutes through the formation of OH-radicals, photomineralization produces CO_2, inorganic sulfate, and nitrogen compounds (such as NH_3 and N_2). Bentazon appears to be resistant to hydrolysis in pH 5, 7, and 9 buffer solutions (U.S. EPA RED, 1994).

Ground water monitoring data (U.S. EPA, 1994) show bentazon occurring in four out of eight states sampled. Concentrations ranged from 0.07 to 120 ppb. The greatest number of detections has been in California, where bentazon was found in 64 out of 200 wells. The detected levels ranged from 0.01 to 20.0 ug/L. The presence of bentazon in ground water is the result of agricultural use. In a study on the leaching of pesticides from golf courses in Florida, bentazon residues were detected in 3 out of 24 wells. Levels ranged from 3.3 to 120 ug/L. A monitoring

project in Virginia showed bentazon concentrations in ground water from 0.07 to 0.547 ug/L. Bentazon residues were detected in 5 out of 12 wells. In Missouri monitoring studies bentazon was found in five wells out of 266 located in agricultural counties. Concentrations ranged from 0.6 to 1.0 ug/L. In four other states, Louisiana, Mississippi, Oregon and Washington, monitoring showed no detections of bentazon in ground water.

More recent (July 1, 1995 through June 30, 1996) sampling for pesticide residues in California well water showed the number of bentazon detections in ground water to be greatly decreased. Bentazon was found in only one well of 1,124 sampled in 37 California counties (DPR, 1997).

Bentazon may contaminate surface waters as a result of its high dissolved runoff potential and its use pattern that involves either direct application to the water or its application to fields just prior to flooding. When used according to good agricultural practice, bentazon applications should not result in any contamination of groundwater and drinking water because of its rapid degradation in plants, and especially in the soil (half-lives of only 3-21 days) (Huber and Otto, 1994).

Food

Bentazon and its 6- and 8-hydroxy metabolites may be found in food as a result of bentazon use in agriculture. In the United States tolerances are currently established on the basis of combined residues of bentazon and its 6- and 8-hydroxy metabolites in or on agricultural commodities. They are listed under 40 CFR & 186.375 as follows:

Commodity	**parts per million (ppm)**
Beans (except soybeans) dried	0.05
Beans (except soybeans) dried, vine hays	3
Beans (except soybeans) forage	10
Beans, succulent (including beans, Lima)	0.5
Bohemian chili peppers	0.05
Corn, fodder	3
Corn, forage	3
Corn, grain	0.05
Corn, fresh	0.05
Mint	1
Peanuts	0.05
Peanuts, hay	3
Peanuts, hulls	0.3
Peanuts, forage	3
Peas (dried)	1
Peas (dried), vine hays	8
Peas, forage	3
Peas, succulent	0.5
Rice	0.05

Commodity	parts per million (ppm)
Rice, straw	3
Sorghum, fodder	0.05
Sorghum, forage	0.2
Sorghum, grain	0.05
Soybeans	0.05
Soybeans, forage	8
Soybeans, hay	8

Tolerances for food items derived from animals are expressed in terms of the combined residues of bentazon and its degradation product AIBA. They are listed under 40 CFR as follows:

Commodity	parts per million (ppm)
Cattle, fat	0.05
Cattle, meat byproducts	0.05
Cattle, meat	0.05
Eggs	0.05
Goats, fat	0.05
Goats, meat byproducts	0.05
Goats, meat	0.05
Hogs, fat	0.05
Hogs, meat byproducts	0.05
Hogs, meat	0.05
Milk	0.02
Poultry, fat	0.05
Poultry, meat byproducts	0.05
Poultry, meat	0.05
Sheep, fat	0.05
Sheep, meat byproducts	0.05
Sheep, meat	0.05

A feed additive tolerance listed under 40 CFR & 186.375 is established for the combined residues of bentazon and its 6- and 8- hydroxy metabolites:

Commodity	parts per million (ppm)
Spelt, mint, hay	4

Probable Routes of Human Exposure

Human exposure to bentazon may occur as a result of occupational/agricultural activities (mixer/loader/applicator) or agricultural/gardening activities performed by non-trained persons such as homeowners and by ingestion of food and drinking water with bentazon residues by the general population. The first two types of activities involve inhalation of dusts or aerosols and dermal contact.

METABOLISM AND PHARMACOKINETICS

Plants

Plants absorb and translocate bentazon from the site of its application. The degree of translocation depends on the plant species. Bentazon is metabolized rapidly, conjugated, and incorporated into natural plant constituents. The metabolism of bentazon in plants involves its hydroxylation at the 6- and 8-position and subsequent conjugation with carbohydrates or fragmentation and incorporation into natural components such as lignin, proteins, and polysaccharide fractions (starch, pectin, hemicellulose, and cellulose). The only metabolites identified in plants were 6- and 8-hydroxybentazon.

Major metabolites and degradation products of bentazon are illustrated in Figure 1 (adapted from Huber and Otto, 1994).

Laboratory Animals

The metabolism of phenyl labeled ^{14}C-bentazon was studied in male and female CD rats (U.S. EPA RED 1994). The compound was administered in the following ways: a) as a single intravenous dose of 4.1 mg/kg, b) as a single oral dose of 3.8 or 205 mg/kg, or c) as a single oral dose of 3.6 mg/kg following a 14-day pretreatment with unlabeled bentazon at approximately 4 mg/kg-day. Absorption from the gastrointestinal tract was about 88.1-95.9% of the dose. The absorbed amount was eliminated in the urine and 0.8-2.3% of the dose was eliminated in the feces over a period of 168 hours. At sacrifice, the total amount of radioactive residues was less than 0.69% of the dose. Parent bentazon eliminated in the urine amounted to 77.37-91.02% of the dose. Two derivatives of bentazon were also found in the urine: 6-OH-bentazon in amounts up to 6.34% of the dose and 8-OH-bentazon in trace amounts up to 0.23% of the dose.

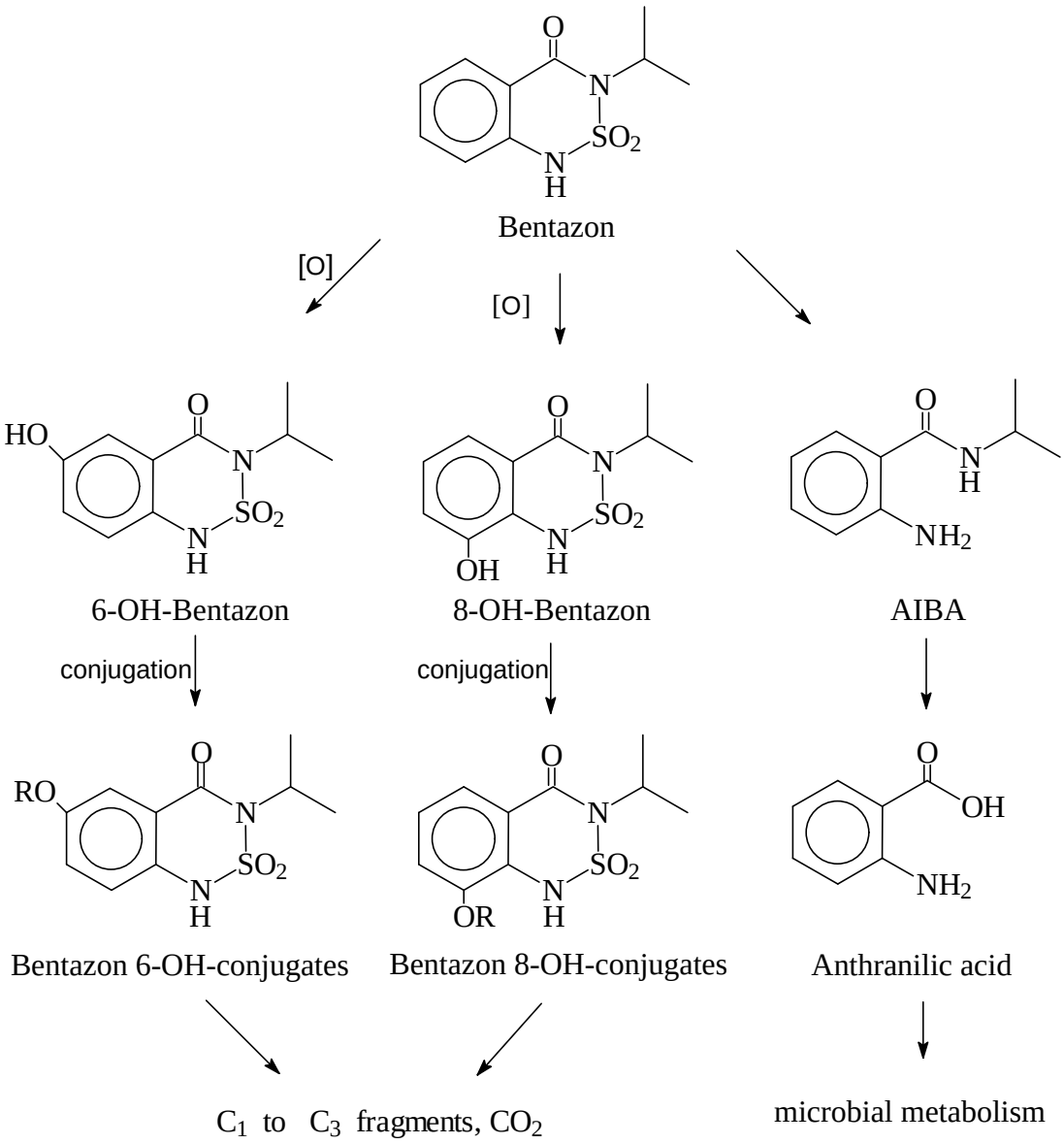


Figure 1. Bentazon and its major metabolites and degradation products (adapted from Huber and Otto, 1994).

Biliary excretion after single oral doses of 4 mg ^{14}C bentazon/kg administered to five male and female rats was, after 24 hours, 1.3% and 0.2% (males and females, respectively) of the administered doses. After a high dose of 200 mg/kg administered orally, 1.8% and 0.8% of the dose was detected in bile after 24 hours in males and females respectively. There was no evidence of bentazon accumulation in rat tissues following either single or multiple doses (Hawkins et al., 1987).

The metabolic pattern of bentazon in rabbits seems to be similar to the one in rats. Three male New Zealand White rabbits were administered 5 mg ^{14}C (labeled in the phenyl ring) bentazon by gelatin capsule. Animals were killed by day six and by that time the total recovery was 93.5% of the administered dose. Excretion in urine during the first 24 hours after dosing was 89.3% of the administered dose and in the feces 3%. GLC analysis of urine showed that unchanged bentazon was the major excreted product. Less than 1% of the administered dose was detected as 6- and 8-hydroxybentazon (combined) (Davies and Rogers, 1974; Otto, 1974).

Sodium bentazon does not seem to penetrate the skin of rats to any significant degree. Only 1-2% of the radioactivity was recovered, primarily in the urine after single topical application of the radioactive sodium bentazon at doses of 0.12, 1.2, 12.0, or 120.0 mg/kg. Most radioactivity was still on the skin at 10 and 72 hours after application. Negligible amounts of radioactivity were retained in the body (Hawkins *et al.*, 1985).

The selected studies described above illustrate the metabolic pattern of bentazon and its sodium salt in laboratory animals. More data on biochemical aspects of bentazon including its absorption, distribution and excretion are presented in Pesticide Residues in Food - 1991 (WHO/IPCS, 1992). Evaluation of all these data leads to the conclusion that after oral administration bentazon is rapidly absorbed, mainly via the stomach, and rapidly excreted, largely unchanged, in the urine. Only a small amount (1-2%) appears in feces over the first 96 hours. As in plants, only two metabolites have been identified in animals, 6-hydroxy- and 8-hydroxy-bentazone, at very low levels. Absorption and excretion in rats and in rabbits are not affected by sex, dose level, or repeated dosing.

Domestic Animals

Three kinds of domestic animals (cows, goats and hens) were used to study the metabolism of bentazon and its major metabolites 6-hydroxybentazon and 8-hydroxy bentazon. The studies with cows suggested that bentazon's products of concern in milk consist of unchanged bentazon and its metabolite 2-amino-N-isopropyl benzamide (AIBA) (U.S. EPA RED, 1994). The more recent metabolism studies with goats and hens showed no residues of AIBA in milk and hens. The only residue product of concern was the parent compound (WHO/IPCS, 1995).

Dairy cows were dosed with [U-^{14}C] bentazon, [^{14}C] 8-hydroxy bentazon, and [^{14}C] 6-hydroxybentazon at 1 ppm, 5 ppm, and 20 ppm in the diet for a maximum of 28 days. The study showed that after oral dosing bentazon is absorbed and eliminated rapidly in the urine. Bentazon and AIBA accounted for the majority of the terminal residues in tissues and milk (U.S. EPA RED, 1994).

The metabolism of bentazon and its major metabolites 6-hydroxybentazon and 8-hydroxybrentazon was studied in lactating goats (WHO/IPCS, 1995).

Two lactating goats were administered 3 and 50 mg/kg bw of [^{14}C] bentazon once a day. The goat receiving 3 mg/kg bw was dosed for five consecutive days and the other one received eight daily doses of 50 mg/kg bw. Bentazon was eliminated mainly in urine (91.4% for the goat receiving 3 mg/kg bw. and 80.6% for the goat receiving 50 mg/kg bw.). There was only 0.6% of the dose determined in feces for the 3 mg/kg bw goat and 5.6% for the other goat. The parent bentazon constituted 71-96% of the total radioactive residues (TRR) in milk, 71-97% in muscles, 94-98% in fat, 91-98% in kidney, 83-84% in liver, 97-100% in urine and 71% in feces. The bile and liver contained bentazon-N-glucuronide in addition to the parent compound. No other metabolites of bentazon were found in the milk or tissues.

In another experiment two lactating goats were administered [^{14}C] 6 hydroxybentazon in feed at concentrations 41 ppm (equivalent of 2 mg/kg-day for goat A) and 973 ppm (equivalent of 40 mg/kg-day for goat B). Goat A received five and goat B six daily doses of [^{14}C] 6 hydroxybentazon. The proportions of the total administered dose excreted with the urine and feces were 69.9% and 86.1% four and twenty four hours after the last dose respectively. A similar experiment was conducted with [^{14}C] 8 hydroxybentazon. The concentrations in the feed were 42 and 732 ppm (no equivalent doses per kg of body weight were provided). The proportions of the total administered dose excreted with the urine and feces were 83.3% and 91.4% 24 hours after the final dose respectively. The radioactive residues measured in various samples in both experiments are shown in Table 3.

Table 3. Total Radioactive Residues in Goat Tissues and Milk after Administration of [^{14}C] 6 hydroxybentazon and [^{14}C] 8 hydroxybentazon ((adopted from WHO/IPCS, 1995).

Sample	TRR, mg/kg as hydroxybentazon			
	From 6-hydroxy		From 8-hydroxy	
	41 ppm[1]	973 ppm[1]	42 ppm[1]	732 ppm[1]
Milk	0.021	0.529	0.023	0.623
Muscle	0.011	0.240	0.012	0.581
Fat	0.027	0.948	0.007	0.396
Kidney	0.140	22.460	0.118	17.720
Liver	0.018	0.915	0.021	2.247

[1] Dosage expressed as equivalent level in feed
The low results for liver were explained by the presence of bentazon N-glucuronide.

In yet another study two groups of lactating goats were maintained on a diet containing 15 ppm of bentazon and 75 ppm of 6-hydroxybentazon (low-level group) and 75 ppm bentazon and 150 ppm of 6-hydroxybentazon (high-level group) for 21 days. One animal from each group was slaughtered at 22, 28 and 35 days after the beginning of dosing. Milk samples were assembled for analysis on days 1, 7, 14, 21, 28 and 35. Bentazon residues in all milk samples were below the detection limit (0.02 mg/kg). Residues of 6-hydroxybentazon from the low-dose group were <0.02 mg/kg in all samples except one with 0.03 mg/kg-day. The residues of 6-hydroxybentazon from the high-dose group ranged <0.02-0.07 mg/kg. There were no residues detectable in milk on the seventh day of the withdrawal period. Less than 0.1% of the applied 6-hydroxybentazon was transferred into the milk.

Limited accumulation and metabolism were demonstrated in studies involving laying hens dosed with [U-^{14}C] bentazon at 100 ppm in the diet for five days. About 80% of the total radioactive residues (TRR) in tissues and eggs were identified as unchanged bentazon; 16% of the TRR in liver consisted of N-glucuronide conjugate of bentazon. The highest total radioactivity at the level equivalent to 1.63 ppm was found in the liver (U.S. EPA RED, 1994)

The more recent studies with hens discussed in WHO/IPCS report (1995) showed that after administration of [^{14}C] bentazon to hens the major radioactive component in extracts of liver, muscles, fat and eggs was the parent compound. Radioactivity measured in liver extracts was associated mainly with bentazon (0.92 mg/kg) and to a lesser degree with its N-glucuronide conjugate (0.12 mg/kg). The excreta contained 45% of the total radioactive residue as bentazon, 12% as its N-glucuronide conjugate, and 15% as 6-hydroxybentazon.

The main residues in the excreta of hens dosed with 6-hydroxybentazon and 8-hydroxybentazon were the unchanged compounds and their glucuronide or sulfate conjugates.

The excretion of radioactivity measured in three groups of laying hens (10 birds/group) dosed with 10 mg/hen-day with [^{14}C] bentazon, [^{14}C] 6 hydroxybentazon or [^{14}C] 8 hydroxybentazon for five days was rapid. The total radioactivity recovered 6 hours after the final dose was 93.6% for the bentazon group, 90.2% for the [^{14}C] 6 hydroxybentazon group and 93.1% for the [^{14}C] 8-hydroxybentazon group. The mean concentrations of radioactivity in all groups were highest in the kidneys, followed by muscles, liver and whole blood.

The Joint Meeting of the FAO and WHO Panel of Experts on Pesticide Residues in Food and the Environment of 1995 (WHO/IPCS, 1995) recommended a change in the definition of the residue of bentazon in animal products. The definition was changed into “bentazon” instead of “bentazon and its metabolites”.

TOXICOLOGY

Ecotoxicology

Bentazon has low acute toxicity for non-target organisms. Its octanol/water distribution coefficient at pH 7 is 0.35. This characteristic precludes any bioaccumulation. Table 4 (adapted from Huber and Otto, 1994) shows some acute toxicity values for non-target organisms.

Table 4. Effect of Bentazon on Nontarget Organisms

Organisms	Results
1. Soil organisms: Microflora (28 d)	no adverse effects on C and N conversion at standard application rates
Earthworms (14 days)	EC_{50}[a] > 1000 mg/kg soil
2. Epigeal fauna: e.g., carabid beetles	not harmful
3. Aquatic organisms:	
Chlorella	EC_{50} = 279 mg/L
Ankistrodesmus	EC_{50} = 47.3 mg/L
Daphnia magna (48 hr)	EC_{50} = 125 mg/L
(reproduction)	NOEC = 120 mg/L
Rainbow trout (96 hr)	LC_{50} = > 100 mg/L
Rainbow trout (extended test)	NOEC[b] = > 48 mg/L
Carp (96 hr)	LC_{50}[c] = > 1000 mg/L
Perch (96 hr)	LC_{50} = > 100 mg/L
4. Pollinators:	
Honeybees (BBA test)	nontoxic to bees
5. Birds:	
Bobwhites (single dose)	LD_{50}[d] = > 1140 mg/kg.
Bobwhites (8 day feeding)	LD_{50} = > 5000 mg/kg.
Mallard ducks (8 day feeding)	LD_{50} = > 5000 mg/kg.

a - concentration causing certain, usually adverse, effects in 50% of a population; b - concentration causing no effect in the observed population; c - concentration causing 50% death in a population in a specified period of time, d - the dose of a chemical causing death in 50% of the exposed subjects.

The results presented in the table show low enough toxicity that there should be negligible effects of bentazon on nontarget organisms in normal use (Huber and Otto, 1994).

Toxicological Effects in Animals

Acute Toxicity

Bentazon was evaluated in a variety of acute toxicity tests. Table 5 presents results of these tests in laboratory animals.

Table 5. Acute Toxicity for Bentazon

Animal	Test	Result LD_{50}	References
Rat (M,F)	Oral	1220 mg/kg (1056-1409)	Hofman, 1973
Rat (M,F)	Oral	1100 mg/kg	Hartley and Kidd,1987
Rat (M)	Oral	ca. 1780 mg/kg	Hildebrand and Kirsch, 1982
Rat (F)	Oral	1470 mg/kg (1080-1919)	Hildebrand and Kirsch, 1982
Rat (M)	Oral	2340 mg/kg (2208-2480)	Toyoshima et al., 1978b
Rat (F)	Oral	2470 mg/kg (2058-2964)	Toyoshima et al., 1978b
Mouse (M,F)	Oral	400 mg/kg	Hartley and Kidd, 1987
Rabbit (M,F)	Oral	750 mg/kg	Zeller and Bernstiel, 1969
Cat (M,F)	Oral	ca. 500 mg/kg	Zeller and Magoley, 1970
Dog (M,F)	Oral	> 100 mg/kg	Zeller and Magoley, 1970
Rat	Dermal	>2500 mg/kg	Spencer, 1982
Rabbit (M,F)	Dermal	4000 mg/kg	Spencer, 1982
Rat (M)	Subcutaneous	970 mg/kg (705-1329)	Tyoshima et al., 1978b
Rat (F)	Subcutaneous	975 mg/kg (813-1170)	Tyoshima et al., 1978b
Mouse (M)	Subcutaneous	655 mg/kg (585-734)	Tyoshima et al., 1978a
Mouse (F)	Subcutaneous	580 mg/kg (550-673)	Tyoshima et al., 1978a

Animal	Test	Result LD_{50}	References
Rat (M)	Intraperitoneal	403 mg/kg (336-443)	Tyoshima et al., 1978b
Rat (F)	Intraperitoneal	407 mg/kg (363-456)	Tyoshima et al., 1978b
Rat (M)	Intraperitoneal	ca. 383 mg/kg	Kirsch and Hildebrand, 1983Rat (F)
	Intraperitoneal	>316<383 mg/kg	Kirsch and Hildebrand, 1983
Mouse (M)	Intraperitoneal	494 mg/kg (437-558)	Tyoshima et al., 1978a
Mouse (F)	Intraperitoneal	505 mg/kg (447-571)	Tyoshima et al., 1978a
Rabbit	Eye irritation	Slight irritation 00072791	U.S. EPA MIRD No.
Guinea pig	Dermal sensit.	Sensitizer	BASF, 1986
Bentazon Sodium Salt			
Rat (M)	Oral	1480 mg/kg	Hofman, 1974
Rat (F)	Oral	1336 mg/kg, acid	Hofman, 1974
Guinea pig	Oral	ca. 1100 mg/kg	Kirsch, 1974
Guinea pig	Oral	1000 mg/kg	Kirsch, 1974

After oral dosing in acute toxicity studies in rats and mice the observed signs of toxicity included dyspnea, apathy, staggering gait, prostration and, in cats and dogs, vomiting. Cats showed also signs of convulsions.

In an oral dose-finding study for testing developmental toxicity in rats (DPR, 1996) early resorptions were seen in the five pregnant rats dosed at 400 mg/kg-day, the lowest dose tested. This could be viewed as a possible adverse effect from a one or two day oral exposure to bentazon, with a LOAEL of 400 mg/kg-day.

Bentazon (50% w/w formulation) applied for 24 hours to the intact and abraded skin of rabbits (3 rabbits/sex) at a dose of 0.5 g resulted in primary irritation. Slight erythema cleared by day eight post dosing (Hildebrand and Kirsch, 1983a).

Bentazon appeared also to be a primary eye irritant. In a study using White Vienna rabbits animals (three rabbits/sex) were given 0.1 ml (ca. 33 mg bentazon) in the conjunctival sac of one eye. Eyes were not washed. The application resulted in corneal opacity, iris congestion, conjunctival redness, chemosis and discharge. The symptoms cleared by day 15 post dosing. This experiment showed bentazon to be moderately irritating (Hildebrand and Kirsch, 1983b).

Sensitizing properties of bentazon were shown in guinea pigs using the Magnusson and Kligman Maximization Test (Kieczka and Kirsch, 1986) and the Open Epicutaneous Test (Kieczka and Hildebrand, 1986).

Subchronic Toxicity

Rats

Among the available subchronic toxicity studies a 13-week dietary study in Wistar rats is considered by the U.S. EPA to be the most appropriate for this type of study since it meets all required standard criteria for testing subchronic effects (Tennekes *et al.,* 1987). In this study ten rats/sex/dose level, approximately eight weeks old, received bentazon in their diet at concentrations of 0, 400, 1200 or 3600 ppm. An additional ten rats/sex were included in the control and 3600 ppm groups, which were retained 28 days beyond the final dose.

According to the U.S. EPA a systemic NOEL (no-observed-effect level, used interchangeably in this document with no-observed-adverse-effect level, or NOAEL, unless specific distinction is made) of 1200 ppm (equivalent to 60 mg/kg-day) was established, based on the adverse effects observed at 3600 ppm (180 mg/kg-day). These effects included reductions in body weight gain, increased thromboplastin and prothrombin times, diuresis, clinical chemistry changes (e.g. increases in albumin, albumin/globulin ratios, and sodium), increased kidney and liver weights, and suggestive evidence in females in the 3600 ppm group of lung thrombi and dilated uterine horns.

Evaluation of this study presented in WHO/IPCS (1992) identifies a NOAEL at 400 ppm (equal to 25.3 and 28.9 mg/kg-day for males and females, respectively). However no convincing arguments are given to justify this scientific judgment. The only support for this NOAEL would be in changes observed in protein electrophoresis patterns in males at 1200 ppm. Without examining the original data it is difficult to advocate the number chosen in the WHO/IPCS (1992) review as more appropriate for the NOAEL than the higher value (60 mg/kg-day) recommended by U.S. EPA (1994).

Another subchronic dietary feeding study with bentazon in rats (Zeller and Kirsch, 1970) can be considered as supplemental information. In this study bentazon was administered in the diet to 20-30 Sprague-Dawley rats/sex/dose level for 90 days at 0, 70, 200, 800 and 1600 ppm. In the "postexposure" part of the experiment, 9-10 rats/sex at dose levels of 0, 70 and 1600 ppm were taken off their bentazon diets after 90 days and given bentazon-free feed for the next six weeks.

No effects in either sex were noted for the following parameters: food consumption (note, no water intake determinations), body weight, the absolute weights and weight-to-body weight ratios for the liver, kidney and heart, urinalysis (note, no volume or specific gravity determinations), platelet counts, prothrombin time (note, activated partial thromboplastin times were not studied), or the incidences of neoplastic and non-neoplastic lesions. Gross

pathology was comparable in all groups. The only treatment-related effects (suggested by DPR, 1996) were the following: increased hematocrit at day ≈30 (1600 ppm males and

females) and at day ≈ 70 (800 and 1600 ppm males; 1600 ppm females) and increased blood urea at day ≈ 30 (800 and 1600 ppm males; 1600 ppm females) and at day ≈ 70 (800 and 1600 ppm males).

According to the WHO/IPCS (1992, p.31) review of the same study, histopathology showed isolated seminiferous tubule and/or testicular degeneration in 2/20 and 1/20 rats at 200 and 1600 ppm at 90 days, and in 1/10 at 1600 ppm after the withdrawal period. However, these changes were not considered to be compound-related.

Rabbits

New Zealand White rabbits (5/sex/dose level) were exposed dermally to 0, 250, 500 or 1000 mg bentazon/day in carboxymethylcellulose (CMC) (4 mL/kg) for 21 day. Daily exposures lasted for six hours and were performed on at least 10% of the body surface (intact shaved skin), under a semi occlusive condition. The results and quality of the experiment are questionable because animals got infected by coccidia. A NOAEL of 500 mg/kg-day seems to be appropriate. It was based on the decreased food intake and body weight reduction, which were not confined to animals with coccidiosis (Schilling et al., 1988).

Dogs

A 13-week study in beagle dogs (Leuschner et al., 1970) was previously used as a basis for the calculation of the Proposed Maximum Contaminant Level for bentazon in California (DHS, 1988). In the study beagle dogs (three dogs/sex/dose) were given bentazon in a diet at concentrations of 0 (control), 100, 300, 1,000 or 3,000 ppm (0, 2.5, 7.5, 25 and 75 mg/kg-day) for 13 weeks. At 3,000 ppm one male and one female dog died, and all surviving animals showed weight loss and ill health.

In addition, at various times during the experiment at the highest dose level the following adverse effects were noted: sedation (starting within one hour after feeding and lasting from two to 24 hours); vomiting; bilateral hemorrhagic conjunctivitis; diarrhea; decreased feed consumption; stomatitis (males only); episodes of tremors and/or ataxia; and hematological effects such as reduction in hemoglobin concentration, red blood cell count and packed cell volume, increased prothrombin time, and decreased platelet count. Serum chemistry effects seen at 3000 ppm level included increased SGPT and SGOT , increased alkaline phosphatase, increased blood urea nitrogen, increased total bilirubin and decreased total protein. Serum electrolyte effects consisted of increased chloride and decreased potassium.

Urinary effects were observed at 300, 1,000 and 3,000 ppm and included traces of ketones, proteinuria, increased potassium, increased sodium, and increased urine specific gravity. Gross pathology effects were seen only in the 3,000 ppm group, consisting of pale liver, liver with marked or maculate lobes, and pale kidneys. Histological effects at the highest tested level can be listed as slight fatty degeneration in the myocardium, slight to marked fatty degeneration in the liver, and prostatitis sometimes involving pus formation in all males in this group. Similar signs of prostatitis were observed in one male each at the 300 and 1,000 ppm levels. The NOAEL established in this study was 100 ppm (2.5 mg/kg-day).

Mutagenicity

A variety of tests are available on the mutagenic potential of bentazon (WHO/IPCP, 1992; U.S. EPA; 1994; DPR, 1996). The tests can be grouped into three classes: testing for gene mutation, chromosome effects, and DNA damage. A summary of genotoxicity testing of

bentazon is presented in Table 6, adapted from the WHO/IPCP (1992) review. All tests assembled by WHO/IPCP (1992) and listed in the table showed a negative response.

Table 6. Genotoxicity testing of bentazon

Test System	Test organism	Concentration	Results	Reference
Rec. assay	*B. subtilis*	20-2000 µg/disc	Negative	Shirasu et al.,1976
Reverse Mutation	*S. typhimurium*[a] TA98, TA100, TA1535, TA1537, TA1538 *E. coli* WP 2 hrs	10-1000 µg/disc	Negative	Shirasu et al., 1976
Host mediated	Mouse *S. typhimurium* G46 i.p.	0-200 mg/kg	Negative	Shirasu et al., 1976
Ames test	*S. typhimurium* TA98, TA100, TA1537	3.1-2000 µg/plate	Negative	Oesh, 1977
CHO/HPTR for point mutation	CHO (Hamster)[a] Substrain K4[a]	0.1-10 mg/mL	Negative Weakly positive	Gelbke and Jackh, 1985
CHO/HPTR for point mutation	CHO (Hamster)[a] Substrain K4[a] subclone BH4	1.25-15 µg/mL	Negative	den Boer, 1985
Micronucleus (bone marrow)	Mouse	200-800 mg/kg	Negative	Gelbke and Engelhardt, 1985
Unscheduled DNA synthesis	Mouse (primary hepatocytes)	2.51-502 µg/mL	Negative	Cifone and McKeon, 1985a
Chromosomal aberrations	CHO cells	1.7-5.0 mg/mL	Negative	Taalmann, 1987

Test System	Test organism	Concentration	Results	Reference
Dominant lethal	Rat (M) (SD)	20-180 ppm In diet (13 weeks)	Negative	Leuschner, 1971
Dominant lethal	Mouse (F) (NMRI)	195 mg/kg bw (single dose)	Negative	Hofman and Peh, 1975
Ames test	*S. typhimurium* TA100, TA1535, TA1537, TA1538 TA98	20-5000 µg/plate	Negative	Gelbke and Engelhardt, 1983b
Ames test	*S. typhimurium*[a] TA1535, TA100, TA98, TA1537, TA1538	20-5000 µg/plate	Negative	Gelbke and Engelhardt, 1983b
Reverse Mutation	*E. coli* WP2uvra	20-5000 µg/plate	Negative	Gelbke and Engelhardt, 1983b
Ames test	*S. typhimurium*[a] TA1535, TA100, TA98, TA1537, TA1538	500-10000 µg/plate	Negative	Gelbke and Engelhardt, 1985
Mitotic gene	*Saccharomyces cerevisiae* diploid strains	100 ppm	Negative	Giebert and Lemperle, 1974
Ames test	*S. typhimurium* TA100, TA98, TA1535, TA1537 TA1538	Up to 5000 µg/plate	Negative	Moriya et al., 1983
Reverse Mutation	*E. coli* WP2 her	Up to 5000 µg/plate	Negative	Moriya et al., 1983

[a] With and without activation
[b] Male

DPR's assemblage of tests performed with bentazon for gene mutation, chromosome effects and DNA damage also showed overall negative results in these categories (DPR 1996). In summary, currently available *in vitro* and *in vivo* genotoxicity data indicate no evidence of bentazon's genotoxic activity.

Developmental Toxicity

Rats

Bentazon was administered by gavage to groups of 25 pregnant rats at dose levels of 0, 40, 100 or 250 mg/kg on days 6-through 15 of pregnancy (Becker et al., 1987 as cited in WHO/IPCP, 1992; U.S. EPA; 1994; DPR, 1996). According to the U.S. EPA (1994) the NOEL for maternal toxicity was over 250 mg/kg-day and the developmental toxicity NOEL was 100 mg/kg-day. This was based on an increase in post-implantation loss characterized by fetal resorptions accompanied by a reduction of body weights of fetuses surviving to day 21 at 250 mg/kg-day (lowest-observed-effect level or LOEL). (The terms LOEL and LOAEL or lowest-observed-adverse-effect level are used in this document interchangeably unless specific distinction is made.) In addition, at the LOEL there was an increased incidence of delayed skeletal ossification. Evaluation of the same study by WHO/IPCP (1992) shows 100 mg/kg-day as a NOAEL for both maternal and fetotoxicity. However, the LOAEL of 250 mg/kg-day for maternal toxicity is not adequately substantiated. It is based on possible decreased maternal food intake, which was slightly reduced at 250 mg/kg-day only on days 6-11. On days 11-16 the trend reversed and food intake increased slightly.

There are at least two other studies in rats, which are of only supplemental value since they do not fully meet current both U.S. EPA and California EPA standards for developmental toxicity testing. In one of these studies four groups of Charles River CD pregnant females were fed diets containing 0, 2000, 4000 or 8000 ppm bentazon from day 0 (day of observed semen in vagina, or detection of copulatory plug) to day 21 of gestation (day of sacrifice). Equivalent doses of bentazon based on food consumption and body weights were 0, 162, 324, and 631 mg/kg-day. There was no indication of teratogenic effects of bentazon at any dose level as determined by external, soft tissue and skeletal examination. The NOAEL for maternal toxicity was 162 mg/kg-day, based on increased water intake and increased amniotic fluid weight at higher doses (Itabashi et al., 1982 as cited by WHO/IPCS 1992). The study is of limited value for risk assessment because individual data were not complete (DPR 1996) and necropsy findings were presented only for one animal (WHO/IPCS 1992).

In another study five groups of pregnant Sprague-Dawley female rats (26-28 per group) were administered by gavage 0, 22.2, 66.7 or 200 mg of bentazon/kg-day. There were no differences among groups in the noticed incidence of any anomalies, such as wavy ribs, accessory ribs, sternal ossification, unilateral renal pelvis enlargement or incomplete skull bone ossification. The NOAEL for this study was > 200 mg/kg-day (Hofmann and Merkle, 1978 as cited by WHO/IPCS, 1992). According to DPR (1996) the study has many shortfalls such as numerous cases of spina bifida in vehicle control, high numbers of late deaths and reduced numbers of fetuses in all groups. The study is of low value for evaluation of developmental effects.

Rabbits

Four groups of pregnant Chinchilla rabbits were administered bentazon at dose levels of 0, 75, 150, or 375 mg/kg-day on gestation days 6-18 (Becker et al., 1987 as cited in WHO/IPCS, 1992; U.S. EPA; 1994; DPR, 1996). According to WHO/IPCS (1992) the maternal toxicity NOAEL in this study was 150 mg/kg-day. It was based on the occurrence in a single doe of a partial abortion, embryonic resorptions, and the absence of living fetuses. The abortion was considered compound-related based on the dose range-finding studies that showed 11.1 and 70% post-implantation losses at 300 and 450 mg/kg bw. The developmental toxicity NOAEL was over 375 mg/kg-day. DPR's evaluation of this study shows the maternal toxicity NOEL of > 375

mg/kg-day and the developmental toxicity NOEL of 375 mg/kg-day. The latter one was based on an increased resorption rate noted at 450 mg/kg-day in a pilot study in absence of maternal toxicity (DPR, 1996). In the light of the non-accessibility of the original dose-range finding studies and absence of details on them in the WHO/IPCS report (1992) OEHHA favors DPR's determination, which seems to be better substantiated.

In another study artificially inseminated Himalayan ChBB:HM rabbits were given bentazon at doses of 0, 50, 100 or 150 mg/kg-day on days 6-18 post insemination (BASF, 1978 as cited in WHO/IPCP, 1992; DPR 1996). A NOAEL of 50 mg/kg-day was suggested by the WHO/IPCP (1992) report based on vaginal hemorrhages and subsequent deaths at 100 and 150 mg/kg-day. There is no indication in the report whether the NOAEL applied only to maternal or to both maternal and developmental toxicities. Evaluation of this study by DPR is different. DPR report (1996) states that the level of bentazon selected in this study was too low and no toxicity was observed in any parameters measured.

The study seems to be at the most of supplemental value. For pesticide registration purposes it was replaced by the study with Chinchilla rabbits (Becker at al., 1987) described above.

Reproductive Toxicity

Bentazon was tested for reproductive toxicity in a two-generation study in Wistar rats (Suter et al., 1989). Animals were fed bentazon in their diet at concentrations of 0, 200, 800 and 3200 ppm (equivalent to approximately 0, 15, 62 and 249 mg/kg-day). F_0 adults and F_1 adults were exposed for 70 days and 123 days respectively before their mating trial; they were exposed for 113-132 days and 166-183 days respectively before they were sacrificed. Premating body weights were statistically reduced only in the F_1 adults in the 3200 ppm group (both sexes). Reduced body weight during gestation and/or lactation was noted with the F_0 and F_1 females in the 3200 ppm groups. Parental toxicity NOEL was 800 ppm and the LOEL was 3200 ppm based on reductions in food consumption and weight gain, and increased incidence of renal mineralization and liver microgranuloma. Reproductive indices pertaining to mating, fertility, fecundity and gestation were not affected by treatments in either mating trial; therefore the true reproductive NOAEL was > 3200 ppm.

The only progeny effect observed was reduced pup body weight in the 800 and 3200 ppm groups for both generations; the reductions were evident starting day 1 (F_{1a} pups) or day 4 (F_{2a} pups) postpartum and were still present at weaning (day 21 postpartum). Progeny NOAEL or the lowest NOAEL identified in this study (some may refer to it as overall reproductive NOAEL) was 200 ppm.

There is another, older 3-generation reproductive toxicity study in Sprague-Dawley rats (Leuschner et al., 1973). This study does not meet the present standards for reproductive toxicity testing but is of supplemental value because its negative results at the highest dose tested, 180 ppm, are consistent with the study described above. Among deficiencies of this older study is lack of data on homogeneity, and stability of dietary concentrations of bentazon; inadequate data on food and water intake (WHO/IPCS, 1992) vague presentation of the statistical methods and results; and incomplete reporting of the necropsy data for the pups as well as the adults (DPR, 1995b). The subject study consisted of four groups of 20 animals/sex/dose level were maintained on diets containing 0, 20, 60 or 180 ppm bentazon. The F_0 parents were bred after 8 and 18 weeks on diet, F_1 parents at 18 and 29 weeks on diet and the F_2 parents at 18 and 28 weeks on diet. From the F_{3b} litters, 20 rats/sex/group were maintained during a developmental period of 9 weeks, and then examined for histopathological changes. Rats used as parents were randomly

selected. Parental rats for the 2nd and 3rd generation were drawn from b litters. Animals not used as parents or for microscopic examination were sacrificed at the end of lactation period at 4 weeks of age and examined macroscopically.

All measured indices such as fertility, viability and lactation were comparable in all groups. The same applies to litter size, incidence of stillbirth, incidence of abnormal pups, pup birth weight, and pup survival to weaning. There were no clinical signs or parental mortality observed during the entire experiment. The NOAEL was 180 ppm, which is consistent with the overall reproductive NOAEL of 200 ppm identified in the 2-generation study discussed above.

Chronic Toxicity

Bentazon was administered in the diet at 0, 100, 400 or 1600 ppm to six beagle dogs/sex/dose for 52 weeks (Allen et al., 1989). Equivalent bentazon intakes at the end of the study were approximately: 0, 3, 13 and 47 mg/kg-day for the males and 0, 3, 12, and 53 mg/kg-day for the females. All dogs survived until the end of the study. One 1600 ppm male had its exposure to bentazon stopped for six days (during the seventh week) when bloody diarrhea and hematology changes were noticed.

According to the U.S. EPA (EPA RED, 1994) a systemic toxicity NOEL was established at 100 ppm (approximately 3.2 mg/kg-day) and the LOEL was at 400 ppm (approximately 13.1 mg/kg-day). Adverse toxicological effects observed at the highest dose tested included clinical signs of toxicity (emaciation, dehydration, loose and/or bloody stools, pale mucous membranes, and reduced activity), hematological changes suggestive of anemia (decreased red cells, hemoglobin and hematocrit, abnormal red cell morphology, and increased reticulocytes, platelets, leukocytes, and partial thromboplastin time), depressed body weight, intestinal inflammation, and congestion of the small intestine and spleen. The anemia appeared to be due to blood loss from the gastrointestinal tract.

Statistical significance (in comparison with the control group) was reached only for decreased total bilirubin, decreased alkaline phosphatase and decreased specific gravity of urine. U.S. EPA set the LOAEL at 400 ppm based on the finding of feces containing red areas in one male at 400 ppm and two males at 1600 ppm. In spite of the lack of statistical significance for the effect noted at 400 ppm, we consider them biologically important and therefore support the EPA determination of 400 ppm as a LOAEL. It is of importance to note that statistical significance might have been achieved in an experiment with a larger number of animals per group. (The protocol for the chronic toxicity study in dogs requires only six animals per group.) In addition, this effect is consistent with bentazon's effects on blood coagulation observed in mice (Takehara et al., 1985) and rats (Zeller and Kirsch, 1970; Takehara et al., 1984) and in a 13-week subchronic toxicity study in dogs (Leuschner et al., 1970).

The study can also be interpreted differently when evaluated solely on the basis of statistical significance. A NOAEL (adverse changes including irreversible effects) and a NOEL (changes likely to be reversible) in this study have been proposed to be at 400 ppm (DPR 1995b, 1996). This NOAEL was based on intermittent hematology changes, decreased spermiogenesis or tubular degeneration in the testes, and possible hormonal imbalance. The hormonal imbalance was evidenced by the glandular proliferation of the mammary gland observed in four females in the 1,600 ppm group. The NOEL was based on decreased total bilirubin, decreased alkaline phosphatase and decreased urine specific gravity.

As stated above, OEHHA's review of the available documentation (DPR 1995, 1996; U.S. EPA RED, 1994) resulted in our support for the lower value for the NOAEL (e. g. 100 ppm or 3.2 mg/kg-day) identified in the study by U.S. EPA. OEHHA scientists are also of the opinion that the lack of ovary data should not disqualify the study (which meets most of the other requirements under FIFRA) for our purposes, in PHG development.

Carcinogenicity

There are three chronic toxicity studies available to evaluate bentazon's potential for carcinogenicity. The ones of significance are the two-year feeding studies in rats (combined chronic toxicity/oncogenicity) and mice (oncogenicity). Both studies were carried out in Japan's Nippon Institute for Biological Science (NIBS). The other long-term feeding study in mice has been summarized in this section but was of limited value because of inadequate reporting.

Rat study In the chronic toxicity/oncogenicity study bentazon was administered in the diet at 0, 200, 800 and 4,000 ppm to 70 Fisher 344 rats/sex/treatment level for up to two years (Takehara et al., 1984). The study included three tests: one main 24-month study and two satellite experiments of 6 or 12 months duration. Each group in the satellite experiment contained 10 males and 10 females. The animals in the satellite experiments were sacrificed at 27 and 53 weeks. The same animals were used to generate 6- and 12-month data on hematology, serum chemistry, urinalysis, and ophthalmology. The main study had 50 rats of each sex per dose group.

There was no effect on survival. The weights of treated animals were ≈92% and ≈87% of the control animals in the male and female 4,000 ppm groups, respectively, between test weeks 53 and 78; no body weight effects were seen in the lower dose groups in either sex.

Water intake increased in a dose-and-time-dependent manner in the 800 and 4,000 ppm groups (both sexes); a lesser effect was observed at six months in the 800 ppm groups in males and females. The specific gravity of the urine decreased in a dose-dependent manner in the 800 and 4,000 ppm groups at six months (both sexes) and 12 months (males).

Blood urea nitrogen increased in a dose-dependent manner in the males at six months and in females at six months in the 4,000 ppm and at 12 months in the 800 and 4,000 ppm groups. Serum glucose decreased in the males at 6 months (200 and 800 ppm), 12 months (4,000 ppm), and 24 months (200 and 4,000 ppm) and in the females at 24 months (200 and 4,000 ppm).

Absolute and relative kidney weights increased at six and twelve months in the 4,000 ppm groups in both sexes. Absolute and relative thyroid weights decreased at six and twelve months in the 800 and 4,000 ppm male groups.

Activated partial thromboplastin times increased in the males at six months (4,000 ppm), twelve months (800 and 4,000 ppm) and 24 months (4,000 ppm) and in the females at twelve months (800 and 4000 ppm). Prothrombin times increased in the 4000 ppm males at six months and twelve months. Platelet counts decreased at six months in the 800 and 4,000 ppm male groups and in the 4,000 ppm female group. Hemoglobin concentration increased in the males at six months (800 and 4,000 ppm) and twelve months (4,000 ppm).

The occurrence of pituitary cysts increased in the 4,000 ppm female group. Effects on eyes and optic nerves were observed in the 4,000 ppm male groups and to a lesser degree also in the 4,000 ppm female group. Clinical observations revealed that 32% (16/50) of the males in the 4,000 ppm main group exhibited enlargement of the anterior chamber of the eye and 26% (13/50) showed opacity. The corresponding incidences in the female 4,000 ppm main group were 6% (3/50) and 2% (1/50). Besides animals affected in the 4,000 ppm groups, only one other animal

(a 200 ppm male) had opacity of the eye. However, clinically affected rats frequently showed other adverse effects such as cataracts, keratitis/corneitis, cloudy eyeball, optic nerve atrophy, optic nerve degeneration and a severe grade of retinal lesions. The pathogenic process suggested by these findings is glaucoma.

Neoplastic changes were observed in rats that either died or were sacrificed in extremis and those that were sacrificed at the termination of the study. No increases in tumor incidence were reported in dosed rats sacrificed at either 6 months or 12 months when compared to control rats. There was an increase in pheochromocytomas of the adrenal glands in females fed 4,000 ppm illustrated by 0/31 (0%) incidences in controls, 2/29 (7%) in the lowest dose group, 2/35 (6%) in the middle dose group, and 3/27 (11%) in the highest dose group. However, this apparent effect of the chemical was discounted because of the lack of the dose response and the number of incidences observed being well within the historical value of 26/203 (13%) reported for this tumor in several different laboratories. Females also showed a slight increase in endometrial polyps 36% in the 800 ppm and 24% in the 400 ppm groups in comparison with a 20% incidence in controls. These incidence rates were not statistically significantly increased. Chromophobe adenomas of the pituitary glands were statistically significantly increased in the females only in the 200 ppm group 18/29 (62%) when compared to 11/13 (35%) in controls. These incidences are not considered to be biologically significant because of the lack of a dose response at higher doses. Overall bentazon was judged to be negative for a carcinogenic response to the two-year exposure in the diet of male and female rats (U.S. EPA, 1998).

The systemic toxicity NOAEL was established at 200 ppm, equivalent to 10 mg/kg-day (lowest dose tested). Adverse effects (described above in detail) were observed at levels of 800 ppm (40 mg/kg-day; LOAEL) and 4,000 ppm (200 mg/kg-day) and consisted of reduction in body weight gain, increases in prothrombin time and partial thromboplastin time, increased water intake, polyuria, increased blood urea nitrogen, increased hemoglobin, decrease in thyroid gland weight, and increase in kidney weight along with reduced urinary specific gravity.

Mouse study In the mouse oncogenicity study bentazon was administered in the diet at 0, 100 400 and 2,000 ppm (males:0, 12, 47, or 242 mg/kg-day; females 0, 12, 48, or 248 mg/kg-day) to 70 B6C3F_1 mice/sex/group for up to two years (Tajima et al.,1984). The study included three tests: one main 24-month study and two satellite experiments of six or twelve months duration. Each group in the satellite experiment contained ten male and ten female animals. The animals (≈10 mice/sex/group) in the satellite experiments were sacrificed at 27 and 53 weeks. The same animals were used to generate six- and twelve-month midcourse data on hematology, serum chemistry, urinalysis, and ophthalmology. The main study had 50 mice of each sex per dose group.

Survival at the end of the study for the male groups ranged from 60 to 72% and for the female groups 70 to 82%. The lowest survival was observed in 2,000 ppm group (both sexes) but the difference was not statistically significant. There was no significant effect on the rate of occurrence of clinical signs, food consumption, water intake or ophthalmology findings in either sex.

There was a statistically significant increase in the specific gravity of the urine for the 400 and 2,000 ppm male groups tested at twelve months and the incidence of occult blood in the urine of three of the ten 2,000 ppm males tested at 24 months. There were no occult-blood cases among the 30 males that made up the other groups.

Prothrombin time (assayed only at 24 months using ≈ 7 mice/sex/group) was statistically increased in the 400 and 2,000 ppm male groups. Statistically significant changes in blood chemistry at 24 months included increases in the albumin/globulin ratio and total cholesterol in the 2,000 ppm male group.

Statistical differences in organ weights included increased absolute pituitary weight at six months in the 2,000 ppm male group and at 24 months in the 400 ppm and 2,000 ppm male groups; increased absolute thyroid weight at 24 months in the 400 ppm male group; increased absolute left kidney weight at 24 months in the 2,000 ppm male group; and increased absolute brain weight at 12 months in the 400 ppm and 2,000 ppm female groups and at 24 months in the 2,000 ppm male group.

The results of histological examination achieving statistical significance for the main groups included increased frequency of hemorrhage in the liver and in the heart in the 2,000 ppm male group; increased frequency of hyperplasia of the pancreatic islet cells in the 400 ppm and in the 2,000 ppm male groups; and increased frequency of calcification in the testes (tunica albuginea, vascular walls, convoluted deferent canal) in the 400 ppm and 2,000 ppm male groups.

Male mice in the control group exhibited a high rate (18%) of circulatory system tumors. A statistical evaluation (Fisher exact test) of histology data from liver sections in mice that were alive for ≥ 1 year showed a dose-dependent increased incidence of nodular hyperplasia in the females (0 ppm, 1/50; 100 ppm, 5/49; 400 ppm, 7/48 [p=0.026]; 2000 ppm, 10/50 [p=0.004]); an increased incidence of nodular hyperplasia in the 400 ppm male group (0 ppm, 12/49; 400 ppm 21/49 [p=0.043]); and an increased incidences of the combination adenoma or carcinoma for the 2000 ppm male group.

The systemic toxicity NOAEL was 100 ppm, equivalent to 15 mg/kg-day (lowest dose tested). Adverse effects as described above were observed at levels of 400 ppm (60 mg/kg-day, LOAEL) and 2,000 ppm (300 mg/kg-day). These effects at the LOAEL level in males were: increased frequency of hyperplasia of the pancreatic islet cells, calcification in the testes and hepatocellular nodular hyperplasia; increased specific gravity of the urine, increased prothrombin time, and increased absolute pituitary and thyroid weights. In the female group at the LOAEL level the adverse effects consisted of increased incidence of hepatocellular nodular hyperplasia and increased absolute brain weight. At the LOAEL level in both sexes there was a slight increase in mortality and reduced body weight.

Among the various adverse effects observed in the 24-month oncogenicity study in mice, effects of particular significance are testicular calcification, hyperplasia of pancreatic islets

and neoplastic changes observed in the liver, lung, and hematopoietic tissues in male and female mice of all groups. Effects produced in the liver were thoroughly evaluated and reevaluated several times by different authors.

Discussion. According to the report by Butler (1985) addressed in the DPR Summary of Toxicology Data for bentazon (1996), the extent of calcification discovered in the limited number of testes examined was slight. However, there was a clear dose-response observed, which reached 70% at the highest dose tested. This finding should not be disregarded in spite of calcification being recognized as a common effect in aging mice. It is likely that this was caused by the administration of bentazon.

A broad review and discussion of the importance of the oncogenic lesions produced in the 24-month test in mice are presented in our previous document on the Proposed Maximum Contaminant Level (PMCL) (DHS, 1988). OEHHA upholds its previous evaluation of the oncogenic effects observed in the mouse study. The following discussion contains slightly modified excerpts related to the mouse study from our PMCL document for bentazon which remain pertinent to our current valuation of the study and interpretation of its results.

The total number of tumors, number of tumor-bearing mice, and number of tumors per mouse in lung and hematopoietic tissues in the treated groups were all similar to those of the control. No statistically significant differences were reported in any of these parameters.

There were two versions of the evaluation of the incidence of hepatocellular tumors identified in this experiment and submitted by BASF to the State of California. Table 7 summarizes the cumulative incidence of hepatocarcinomas and hepatocellular nodule according to two different assessments.

Table 7. Combined Incidence of Hepatocarcinomas and Hepatocellular Nodules in the 2-Year Bentazon Mouse Study According to the Original Report and Subsequent Reevaluation

	Number of Animals			
	Original Report		Reevaluation	
Group	Male	Female	Male	Female
Control	6	4	9	3
100 ppm	10	1	7	1
400 ppm	13	9	8	5
2000 ppm	21	1	10	1

The original evaluation performed by NIBS Lab showed a dose-response relationship in the combined incidence of hepatocarcinomas and hepatocellular nodules in male mice. In the subsequent reevaluation, additional hepatocarcinomas in the controls and fewer malignant lesions in the treated groups were diagnosed. Table 8 illustrates the differences in the diagnosis for male mice which lead to a difference in the overall reported tumor incidence.

Table 8. Comparison of the Two Diagnoses of Liver Changes in Male Mice in the 2-Year Bentazon Study

Group	# of Animals	Original Report	Reevaluation
Control	3	Neoplastic nodule	Carcinomas
100 ppm	3	Carcinoma	Non-carcinomatous nodule
400 ppm	3	Carcinoma	Non-carcinomatous nodule
2000 ppm	11	Carcinoma	Non-carcinomatous nodule

In order to resolve the different interpretations of the Nippon Institute mouse oncogenicity bioassay performed for BASF, additional histopathological evaluations were performed. An independent blind review of the slides was made by three well-qualified pathologists from the U.S. (W. Carlton), U.K. (H. Butler), and Japan (J. Yamate) (Carlton et al., 1987). All three pathologists examined all the liver slides; in addition, Drs. Butler and Carlton examined all lung tissues for male and female mice. Individual and summary data were provided for lung and liver findings. Specified criteria were described for classification of major liver findings. Significant histological features considered are listed below.

Hepatocellular nodular hyperplasia: "The important histologic feature for differentiation of this lesion from hepatocellular adenoma is the preservation of the lobular architecture, albeit markedly distorted, in the nodule…."

Hepatocellular adenoma: "...these variably-sized nodular lesions lack the lobular architecture of the hyperplastic nodule..." (portal tracks and central vein are not integral parts of the altered tissue; compression is a typical feature).

Hepatocellular carcinoma: "These hepatoproliferative lesions vary in size, and have a distinct trabecular pattern of the cellular cords."

The individual diagnostic terms used by the three pathologists were somewhat different, but their findings in the blind reading were very consistent. Their diagnoses of hepatocellular carcinomas were virtually identical. For hepatocellular adenomas they used the following different terms: a) "hepatocellular adenoma" (Carlton); b) "nodule without structure" (Butler); c) "adenomatus nodule" (Yamate). However, notwithstanding different terminology the identification of lesions was strikingly alike. This applies to both hepatocellular adenoma and nodular hyperplasia.

Table 9 summarizes these evaluations of the male liver lesions. The table presents Dr. Carlton's evaluation but is reflective of the evaluations performed by both of the other pathologists.

Table 9. Incidence of Selected Hepatocellular Lesions in Male Mice in the 2-Year Bentazon Study (based on Dr. Carlton's diagnosis submitted to BASF, 3/10/87)

	Dose Group (ppm)			
Diagnosis	0	100	400	2000
Hepatocellular nodular hyperplasia	14	19	21	10
Hepatocellular adenoma	4	3	6	11
Hepatocellular carcinoma	8	7	10	11

It is evident from the table that there is no significant increase in the incidence of hepatocellular carcinomas. This blind reading did not confirm the dose-related increase in hepatocellular carcinomas indicated in the original report. However, there still may be an increase in hepatocellular tumors, primarily adenomas.

The U.S. EPA (1998) recently addressed the relevance of the liver neoplastic findings in the mouse study. It was concluded that the historical control data for liver tumors in $B6C3F_1$ mice provide evidence that there was no significant increase in the incidence of hepatocellular carcinomas or adenomas in the subject study, even though a trend test was shown to be positive.

The highest increase in adenomas was observed in male mice at the 242 mg/kg-day dose level. There were 12/58 (21%) incidences of hepatocellular tumors at this level in comparison with 5/58 (9%) in the concurrent control group. This increase approached the lowest level of statistical significance ($p<0.05$) due to the low incidence of hepatocellular adenomas in the concurrent control group. However, the incidence of adenomas for the male mice at the level of 242 mg/kg-day (12/58 equivalent of 21%) was still below the historical control values (13/60-33/60, equivalent of 26-66%); therefore it can be considered biologically insignificant.

There was no dose-response in the carcinoma incidence in the mouse study. However, the combined frequencies of adenomas and carcinomas were statistically significantly increased in the subject study as shown: 0 ppm, 14/58 (24%); 100 ppm, 12/58 (21%); 400 ppm, 20/59 (34%) and 2000 ppm 23/58 (40%). These combined incidences in the study were also below the

combined incidences of adenomas and carcinomas seen in the historical control data where the range of the rate of occurrence was 19/60-48/60 (31.6-80%).

In the light of the historical control data on the high occurrence of liver tumors in $B6C3F_1$ mice, the rate of neoplastic liver lesions produced in the above-discussed study seems to be biologically insignificant and inappropriate for risk assessment.

Table 10 below summarizes the female liver and lung lesions from Dr. Carlton's evaluation, which is also reflective of the evaluations performed by the other two pathologists. The re-reading of female liver slides re-affirmed a dose-related increase in hepatocellular nodular hyperplasia. The findings presented clearly show no treatment effect on hepatocellular adenoma or carcinoma incidence. The rate of occurrence of bronchoalveolar adenomas in different female groups is not statistically significant and shows no evidence of a trend.

Table 10. Incidence of Selected Hepatocellular and Lung Lesions in Female Mice in the 2-Year Bentazon Study (based on Dr. Carlton's diagnosis submitted to BASF, 3/10/87)

	Dose Group (ppm)			
Diagnosis	0	100	400	2000
Hepatocellular nodular hyperplasia	1	5	8	10
Hepatocellular adenoma	2	0	0	1
Hepatocellular carcinoma	3	1	6	1
Bronchoalveolar adenomas	2	4	1	7

There is another long-term feeding study in mice which can be considered only of supplementary value because of numerous limitations in the design of the study and the pathological examinations (Hunter et al., 1978).

In this study four groups of 40 CFLP mice/sex/dose level were fed diets containing 0, 100, 350 or 1600 ppm of bentazon. No overt signs of toxicity were observed in any group of mice. Histopathological examination was limited to gross lesions, lymph nodes, liver, spleen, thyroid, pituitary and ovaries. The examined tissues did not indicate any bentazon-related tumor induction, but the limited number of tissues examined does not permit an overall assessment of carcinogenicity.

Conclusion on bentazon potential for human carcinogenicity Bentazon has not been studied for its toxic or carcinogenic potential in humans. The only indication of its oncogenic effect comes from the findings of benign liver tumors in mice in a single study. The apparent increase in hepatocellular neoplasms in males in (at least) the 2000 ppm group is primarily the result of an increased incidence of adenomas. There is no evidence for progression to carcinomas nor there is confirmation of a carcinogenic potential from dosed females in that study or from the males and females in a rat study. In addition overall results on mutagenic potential of bentazon are negative in all three test types, for gene mutation, chromosomal aberrations and DNA damage.

Bentazon is not likely to be carcinogenic to humans via all relevant routes of exposure. It was classified by the U.S. EPA as a "Group E" carcinogen which indicates evidence of noncarcinogenicity for humans (Health Effects Division Carcinogenicity Peer Review Committee, 6/26/91). This weight-of-evidence judgment is largely based on the absence of significant tumor increases in chronic rodent studies and the lack of supportive positive findings in mutagenicity tests.

Toxicological Effects in Humans

There are practically no data available on human toxicity. The only information is that reported by Morgan (1982, 1989) who stated that on injection bentazon has caused vomiting diarrhea, dyspnea, tremors and weakness and that it is suspected of being irritating to eyes and respiratory tract. The author did not provide any details to support these statements.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Review of the currently available toxicological data on bentazon indicates that the dose-response assessment should be based on noncarcinogenic adverse effects. The most appropriate study currently available for this purpose is the one-year-dog chronic toxicity study (Allen et al., 1989). This study identifies the lowest NOAEL (3.2 mg/kg-day) among all currently available long -term studies. Because of its longer duration (one-year chronic study) than the previous subchronic study (13-week) used for risk assessment, it is more reflective of lifetime human exposure and allows a decrease of the uncertainty factor from 1000 to 100. The study is discussed in detail in a previous section of this document.

The NOAEL of 3.2 mg/kg-day identified in the study is based on adverse effects at the two higher doses of 13.1 and 47 mg/kg-day. These effects included clinical signs of toxicity (emaciation, dehydration, loose and/or bloody stools, pale mucous membranes, and reduced activity); hematological changes suggestive of anemia (decreased red cells, hemoglobin and hematocrit, abnormal red cell morphology, and increased reticulocytes, platelets, leukocytes, and partial thromboplastin time); depressed body weight, intestinal inflammation, and congestion of the small intestine and spleen.

The choice of the one-year chronic dog study as the most suitable for calculating the PHG results in values different than previously recommended. At that time of our PMCL document for bentazon (DHS, 1988), the results from the one-year dog chronic toxicity study were not yet available. The PMCL was based on a subchronic toxicity study in dogs which was determined to be the best study available to calculate a health standard at that time. The resulting PMCL value (DHS, 1988) was 18 ug/L. The federal Lifetime Health Advisory (Lifetime HA) of 20 ug/L (rounded from 18 ug/L) recommended at the same time was also derived from the subchronic toxicity study in dogs. The same value of 20 ug/L calculated in the same way was recommended as a Maximum Contaminant Level Goal (MCLG), a non-enforceable concentration of a drinking water contaminant that protects against adverse human health effects and allows an adequate margin of safety.

Carcinogenic Effects

Overall evaluation of the available database on bentazon indicates that it is not likely to be carcinogenic to humans because of the absence of significant tumor increases in chronic rodent studies and the lack of supportive findings in mutagenicity tests.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for chemicals in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{NOAEL/LOAEL \times BW \times RSC}{UF \times L/day}$$

where,

NOAEL/LOAEL	=	No-observed-adverse-effect-level or lowest-observed-adverse-effect-level
BW	=	Adult body weight (a default of 70 kg for male or 60 kg for female)
RSC	=	Drinking water relative source contribution (usually in the range of 20% to 80%)
UF	=	Uncertainty factors (typical defaults of 10 to account for inter-species extrapolation, 10 for uncertainty from the subchronic nature of the principal study and 10 for potentially sensitive human subpopulations)
L/day	=	Adult daily water consumption rate (default of 2 L/day)

Calculation of a public health-protective concentration (C, in mg/L) for bentazon in drinking water based on noncarcinogenic endpoints is presented below:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times L/day} = \frac{3.2 \times 70 \times 0.2}{100 \times 2} = 0.22 \text{ mg/L}$$

C = 0.2 mg/L (rounded) = 200 ppb

where,

NOAEL	=	No-observed-adverse-effect-level, approximately 3.2 mg/kg-day
BW	=	Adult body weight of 70 kg
RSC	=	Relative source contribution of 0.2 (default value)
UF	=	Uncertainty factors of 100 (10 to account for inter-species extrapolation and 10 for potentially sensitive human subpopulations
L/day	=	An adult daily water consumption rate of 2 L/day

Thus a PHG of 0.2 mg/L (200 ppb) is developed for bentazon in drinking water. This PHG is calculated based on the NOAEL of 3.2 mg/kg-day for non-carcinogenic effects such as clinical signs of toxicity, hematological changes, depressed body weight and intestinal disturbances identified in a chronic dog study (Allen et al., 1989) at the LOAEL of 13.1 mg/kg-day. Our recommended PHG value is about 11 times higher than the current MCL value of 18 ppb for this compound. The availability of the chronic study allowed a substantial decrease in the uncertainty factor, compared to the subchronic dog study used earlier to estimate a safe exposure level.

RISK CHARACTERIZATION

There are no human toxicity data available on bentazon. However, its animal toxicology database is adequate for calculating a PHG.

The primary sources of uncertainty in the development of the PHG for bentazon in drinking water are the general issues of uncertainty in any risk assessment, particularly inter- and intra-species extrapolation and the relative source contribution (RSC) for bentazon in drinking water, versus other exposure sources. Other uncertainties worth mentioning are those related to the quality of the currently existing database. These, in general, would include the lack of human data and specifically data on the metabolism and mechanism of action of bentazon in humans. In addition, little is known about whether there are certain groups more sensitive to bentazon than are average adults. The PHG of 200 ppb was calculated on the basis of non-carcinogenic effects including clinical signs of toxicity, hematological changes, depressed body weight and intestinal disturbances identified in a chronic dog study (Allen et al., 1989).

In developing a PHG for bentazon we followed current U.S. EPA drinking water risk assessment methodology, including recommended default values for uncertainty factors, body weight, water consumption rate and RSC. The use of a value of 2 L/day for drinking water consumption reflects our interpretation that bentazon in water would not provide significant additional dermal and inhalation exposures in household uses such as showering. We used a standard default value of 20% for RSC assuming the remaining 80% of exposure comes from sources other than drinking water, mainly bentazon residues in food. In recent years bentazon has rarely been found in California ground (drinking) water (DPR, 1997), and thus the major source for human exposure is from residues in food. Our judgment that the PHG should be derived from non-carcinogenic effects of bentazon is consistent with its classification as a “Group E” carcinogen by U.S. EPA.

The PHG of 200 ppb should be adequate to protect sensitive subpopulations, including infants and children, from adverse health effects of bentazon in drinking water.

OTHER REGULATORY STANDARDS

Bentazon is not currently regulated under the Safe Drinking Water Act (SDWA). A Maximum Contaminant Level (MCL), which is the maximum permissible level of a contaminant in water delivered to any user of a public system, has not been established for bentazon by U.S. EPA. However, the U.S. EPA Maximum Contaminant Level Goal (MCLG), a non-enforceable concentration of a drinking water contaminant that is intended to be protective against adverse human health effects, allowing an adequate margin of safety, is currently 20 ug/L. The same value of 20 ug/L is at present calculated for a lifetime drinking water health advisory (HA) (U.S. EPA, 1996). However, according to the U.S. EPA, these two standards will likely be increased to 200 or 220 ug/L (200 or 220 ppb) because the Office of Pesticide Programs has now a complete data base which permits the reduction of the uncertainty factor in the reference dose calculation from 1,000 to 100 (U.S. EPA RED, 1994).

The current California MCL of 18 ug/L (18 ppb) established for bentazon in 1988 after OEHHA's recommendation (DHS, 1988; Lam et al., 1994) was also based on a subchronic study which is now superseded by the more appropriate chronic study. The use of chronic rather than subchronic studies for risk assessment purposes allows a decrease in the uncertainty factor by 10 fold.

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